

Clinical and Experimental Observations in Heart Transplantations

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ORTHOTOPIC CARDIAC allotransplantation has been under study in this laboratory since 1963. Some of the major findings emerging from experience in 155 laboratory allografts and two clinical trials are reviewed in this report.

SURGICAL TECHNIC

As described previously,^{1,2} this was a modification of the Lower-Shumway method.³ In brief, pairs of puppies were chosen on the basis of approximate match in weight, anesthetized and subjected to hypothermia of 15 to 20°C. for the recipient, and 25 to 30°C. for the donor. The excised donor heart was stored in isotonic solution at 4 to 10°C. while preparation of the recipient was completed. The recipient's chest was opened bilaterally through the anterior fourth intercostal space. After complete circulatory arrest by inflow-outflow occlusion the heart was excised by transecting the pulmonary artery and aorta close to the valves and by severing the auricles close to the ventricles. To implant the donor heart, a continuous over-and-over suture was used to approximate the auricular walls and septum. The recipient's aorta and pulmonary artery were then joined to the donor vessels. Reestablishment of circulation by cardiac massage, controlled respiration, blood replacement, treatment of metabolic acidosis,

and rewarming were commenced simultaneously.

INTRAOPERATIVE AND POSTOPERATIVE PROBLEMS

Observations in a series of 107 direct puppy transplants will illustrate the problems of the technic described. Sixty-seven puppies survived for more than one day. Among the 40 animals dying within the first 24 postoperative hours, causes of death included early graft failure due to air embolism or inadequate graft protection (15 puppies), brain damage evidenced by opisthotonus, convulsions, and dilated pupils (10), respiratory failure (4), metabolic acidosis (3), hemorrhage (2) and technical errors (6). In only 5 of the 107 cases were the hearts not resuscitatable.

Cerebral lesions, which accounted for one-fourth of the early deaths, theoretically can result from undue prolongation of the period of circulatory arrest or from inadequate oxygenation during rewarming and cardiac massage. Comparison with the neurologically intact puppies that lived for more than one day indicated that the time limit for circulatory arrest at 15 to 20°C. rectal temperature is one hour. To ensure adequate perfusion during rewarming, cardiac massage should be performed at a rate of 80 per minute with a peak systolic blood pressure of more than 40 mm. Hg. We learned that if these conditions could not be obtained, it was advisable to stop the rewarming process and to administer blood and bicarbonate until the peak systolic pressure reached an adequate level;

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rewarming was then resumed.

Serial arterial blood samples taken during the operation in six puppies (five of which survived the procedure for more than 24 hours) indicated a decrease in pH and base excess to levels of 6.90 and -25 mEq./L., on the average, after rewarming. In six similarly studied dogs given bicarbonate, 5 mEq./Kg. body weight, the decrease in pH and base excess was no longer present at the end of rewarming.

The over-all experience suggested that intraoperative and early postoperative complications might be minimized by an expeditious surgical technic emphasizing adequate graft protection and meticulous administration of anesthesia and artificial respiration, in addition to painstaking postoperative care—in short, by meeting the requirements applicable to any cardiac surgery on infants.

LATE POSTOPERATIVE PROBLEMS

Among the 67 puppies undergoing direct transplants that survived more than 24 hours, 42 died of pulmonary complications, 13 of acute graft rejection, 3 of brain damage, 2 from stricture of the right atrial suture line, 1 from hemorrhage and 5 from miscellaneous causes. One animal was alive and well more than 19 months after the operation; during this period its body weight increased by 18 Kg.

Postoperatively, all animals were given antibiotics. Thirty-seven did not receive immunosuppressive treatment (ISD), 40 routinely were given ISD starting on the third postoperative day, and 30 underwent such treatment only when there was ECG evidence of graft rejection. The ISD regimen included methylprednisolone, 5 or 10 mg./Kg. body weight, and azathioprine in the same dosage. During rejection crises, actinomycin-C, 8 μ g./Kg. was administered. In the group given no ISD, 39 per cent survived more than one week, and 13.5 per

cent more than three weeks. Of animals given ISD routinely, 32.5 per cent were alive after one week, and 15 per cent after three weeks. In the group in which ISD was administered only upon the appearance of signs of rejection, 33.3 per cent were living after one week, and 10 per cent after three weeks.

In individual cases it was evident that ISD suppressed ECG manifestations of rejection. There was, nevertheless, no difference in survival rate between treated and untreated groups. This may be related to the high incidence of infection in these animals, to which the ISD contributed. The incidence of pulmonary infection, whether associated with rejection or not, was higher in animals given ISD (70 per cent) than in those not treated (58 per cent). However, there were fewer deaths due to acute rejection in the treated animals (15 per cent) than in the others (25 per cent).

This experience confirmed the value of ISD administration, but it also underscored the severity of the problem of infection. The measures required to prevent the occurrence of this complication, isolation and aseptic technic, are executed only with difficulty in the animal laboratory.

DELAYED TRANSPLANTS

Since our study of canine homotransplantation was begun, 38 puppy hearts excised while beating and stored for as long as 24 hours under hypothermic-hyperbaric conditions have been transplanted.^{4,5} The best results were gained using O_2 pressures of 3 to 4 atmospheres during storage at 2 to 4°C. Thirteen of 17 hearts stored for 24 hours in this manner were transplanted and resumed function. The longest survivor in this group lived five days. Seven hearts stored for 12 hours were all resuscitated after implantation. The longest survival in this group was 35 days. These observations suggested that hearts can safely be stored

under hypothermic, hyperbaric conditions for as long as 12 hours.

Storage of beating hearts under normothermic conditions was studied in order to gain experience with resuscitation of cadaver hearts and with assessment of the graft's functional capability.^{6,7} A previously reported perfusion system⁶ was used in which 5 L./min. of an O₂-CO₂ mixture was delivered to a disc oxygenator at a constant pressure of 40 mm. Hg. Twenty-six hearts were allowed to remain anoxic at body temperature for 30 to 90 minutes after cessation of ECG activity following asphyxiation and then perfused. All organs resumed beating, and 23 hearts anoxic for 30 minutes and 2 anoxic for 60 minutes demonstrated good myocardial contractility and normal ECG findings. However, one heart resuscitated after 90 minutes of anoxia had poor contractility and its ECG voltage was low.

Of the 23 hearts anoxic for 30 minutes, 13 were studied during isolated perfusion. In four of these hearts, perfusion with whole blood permitted maintenance of sinus rhythm for four hours, on the average; in another four, the use of hemodilution (average hematocrit, 22 per cent) extended the average duration of sinus rhythm to 5.8 hours. The inclusion of a microfilter in the arterial line of the perfusion circuit in five experiments further extended this interval to a mean of 11.6 hours and greatly improved flow through the coronary sinus.

Ten of the hearts anoxic for 30 minutes were transplanted after perfusion for varying periods. Two perfused with whole blood for one and two hours performed poorly during three and five hours for which the hosts survived. Three hearts perfused with the hemodilution technic for one, two and three hours performed well, initially; survival times were seven days, eight hours and one hour, respectively. Five

hearts perfused with the hemodilution-microfiltration method for two, four, six, eight and ten hours all performed well immediately after implantation; survival periods here were two hours, seven days, two hours, six hours and 24 hours, respectively.

These data suggested that the technic utilizing hemodilution and microfiltration of the perfusate was feasible for preservation of the graft and permitted resuscitation 30 minutes after electrical asystole. The successfully transplanted hearts all had normal ECG's during perfusion and exhibited strong ventricular contractions.

CLINICAL OBSERVATIONS

Although our experiences with clinical cardiac transplantation will be reported in greater detail elsewhere, a résumé of our cases may be of interest here.

Case 1

On November 18, 1967, a male infant weighing 2600 Gm. was delivered in our hospital. Sixteen hours after birth the infant was dusky in color, and there was circumoral cyanosis which became more marked with crying. On the next day the diagnosis of complete right-to-left shunt at the atrial level, probably due to tricuspid atresia, was made by cardiac catheterization and angiocardiology.

At this time, it was agreed to attempt cardiac transplantation. A suitable donor could not be found. When the patient was 63 hours old a 4 mm. anastomosis was constructed between the ascending aorta and the right pulmonary artery as a palliative measure. The cardiac anatomy could not be explored because of the patient's poor condition.

For the first three days thereafter, the patient remained critically ill, but after a few days there was slight improvement. However, the infant's weight remained at about 2500 Gm., and chest x-rays disclosed

progressive cardiac enlargement.

On December 4, an anencephalic infant became available. Clinical examination, ECG and chest x-rays failed to demonstrate any cardiac abnormalities. Both the potential donor and the recipient had the same major blood groups and a compatible crossmatch. Lymphocyte histocompatibility studies using the irradiated hamster test also pointed to a good match. The donor ceased spontaneous respiration at 11:30 p.m. on December 5, and assisted endotracheal ventilation was instituted. Cooling of both recipient and donor was started at approximately 3:45 a.m. on December 6. The donor was heparinized during cooling. At 4:25 a.m., the donor's cardiac activity ceased. The heart was immediately excised and immersed in 5°C. normal saline solution. The organ manifested no gross abnormalities. Thoracotomy on the recipient was begun at 4:25 a.m., when his body temperature had reached 19°C. At 4:38 a.m., manipulations induced ventricular fibrillation. Massage was given until cardiectomy at 4:45 a.m. The body temperature at this time was 17°C. Implantation of the donor heart was begun at 4:48 a.m. The anastomoses were completed at 5:20 a.m. and massage was then instituted. The duration of circulatory arrest was approximately 40 minutes.

Rewarming was then carried out. At 5:30 a.m., spontaneous sinus rhythm was resumed. Manual cardiac massage was continued until the temperature had reached 26°C. Strong ventricular fibrillation then developed. Electrical defibrillation restored regular ventricular contractions in sinus rhythm at a rate of 80 to 85 beats per min. The aortic-right pulmonary artery anastomosis was then ligated. When the patient's body temperature had reached 32°C., the chest was closed. The patient was moved to an isolation area at 7 a.m. with a body temperature of 36°C., stable vital

signs, and a heart rate of 90 to 110 per minute. Because of weak respiratory action, assisted ventilation was necessary. Spontaneous movement of the extremities was noted.

During the next few hours, the patient's temperature fell to 33.2°C. In addition, a profound metabolic and respiratory acidosis developed, despite treatment. At 12:10 p.m., bradycardia suddenly appeared. By 12:15 p.m., there was no cardiac rhythm. All attempts at resuscitation were fruitless, and the patient was pronounced dead at 1 p.m. on December 6.

Autopsy later that day showed diffuse areas of atelectasis in the lungs. The donor heart was normal in size and structure and all suture lines were intact. The aortic-pulmonary artery anastomosis had not been completely closed, as the shunt was patent. Examination of the recipient's excised heart disclosed a severe Ebstein's malformation of the tricuspid valve and membranous subvalvular pulmonic stenosis.

Case 2

The recipient was a 57-year-old male with clinical diagnoses of atherosclerotic heart disease, left ventricular myocardial failure and pulmonary hypotension secondary to the left ventricular failure, as well as mild diabetes. The patient was unable to walk more than a few steps without complaining of angina and dyspnea, and neither medical nor surgical therapy offered any hope of reversing his progressive cardiac failure.

On January 9, 1968, a previously healthy 29-year-old, 90 lb. woman was admitted. Her referring physicians reported that she had been comatose for 19 hours and that for the nine hours preceding transfer she had required assisted ventilation. A cardiac arrest of indeterminate duration 8 hours prior to transfer had been managed by external cardiac massage. On admission both pupils

were dilated and fixed bilaterally and she was completely areflexic and unresponsive to any stimuli. An electroencephalogram showed no cerebral cortical activity. A 12-lead ECG disclosed sinus tachycardia with nonspecific ST segment changes. The neurological diagnosis was posterior fossa tumor with herniation through the foramen magnum.

Three hours after admission, the patient's blood pressure began to fall despite increasing doses of vasopressors. At 1 p.m., effective cardiac action ceased. At 1:10 p.m., cardiectomy was performed in the same manner as in the animal studies. At 1:16 p.m., the aorta of the donor heart was cannulated and the coronary arteries were perfused with a hemodilution technic at an average temperature, pressure and flow of 29.1°C., 48.7 mm. Hg and 42.9 cc./min., respectively, for 36 minutes while the recipient was being prepared.

With the recipient under endotracheal anesthesia, the superior and inferior venae cavae were exposed and cannulated through a right atrial incision with concomitant cannulation of the right femoral artery. Cardiopulmonary bypass was instituted utilizing a disc oxygenator (average temperature, 31.9°C.; average flow rate, 4206 cc./min.). After cardiectomy, leaving generous margins of the posterior atrial wall, the donor heart was implanted; a double layer of sutures was used for the aortic anastomosis.

Total cardiopulmonary bypass time was four hours and 41 minutes. Operative perfusion time was 2 hours and 29 minutes, with 2 hours and 12 minutes for support perfusion. At completion of the surgical procedure and discontinuation of support perfusion, the transplanted heart was beating spontaneously and was able to support the circulation of the recipient. However, manifestations of progressive cardiac failure ensued. Phase-shift intraaortic balloon

pumping⁸ temporarily supported the left ventricle, but effective cardiac action ceased eight and one-half hours following surgery.

At necropsy, the recipient's excised heart weighed 550 Gm. The left ventricle was a diffuse fibrotic sac, and its myocardium was thinned to approximately half the normal thickness and contained multiple areas of fibrous scarring. There was diffuse coronary sclerosis with multiple areas of narrowing. The donor heart weighed 250 Gm. There were areas of subepicardial hematoma, probably of recent onset. All suture lines were intact. There was a tumor in the posterior fossa of the brain.

COMMENT

The important points in our laboratory experience seemed to us to comprise the following: (1) Cardiac homotransplantation can be carried out with a reasonable risk for the recipient. (2) The excised donor heart can almost invariably be resuscitated. (3) Immune reactions can be managed with present day drugs. (4) A transplanted heart, although denervated, is able to maintain adequate circulation. (5) Cadaver hearts anoxic for 30 minutes can be resuscitated and successfully transplanted after isolated coronary perfusion.

The failure in the first clinical case probably resulted from the combination of inability to maintain adequate respiration or normal body temperature and inability to correct severe metabolic and respiratory acidosis, despite vigorous treatment. In the second case, the poor performance of the heart was probably related to several preoperative episodes of hypotension and hypoxia, and possibly to the vasopressor treatment that the donor had received prior to the final cardiac arrest. It was also possible that the 36 minutes of isolated perfusion had caused additional damage.

Further clinical trials of heart transplantation, now being undertaken in numerous

centers throughout the world, may be expected to establish the ultimate place of

this operation in the treatment of heart disease.

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